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CLINICAL STUDY

Diagnostic value of the preoperative platelet/lymphocyte ratio and red cell distribution volume in patients with renal masses

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ABSTRACT
OBJECTIVES: Inflammatory markers indicate immune system responses.
BACKGROUND: We retrospectively explored whether the platelet/lymphocyte ratio (PLR), neutrophil/lymphocyte ratio (NLR), and red blood cell distribution width (RDW) were predictive of malignant disease.
MATERIAL AND METHODS: Between 2019 and 2023, 148 patients diagnosed with malignant and benign renal tumors via imaging or biopsy were included. Of these tumors, 117 were malignant and 31 were benign. Blood samples were taken for calculation of the NLR, PLR, and RDW prior to renal biopsy or operation.
RESULTS: The NLR, PLR, and RDW did not differ significantly between patients with malignant and benign renal masses (all $p > 0.05$). The PLR significantly increased with the T stage of malignant masses ($p = 0.011$). According to the T stage, the RDW cutoff was 45.7, the sensitivity was 40 %, and the specificity 82.4 %; the respective values for PLR were 134.9, 70 %, and 70.5 % ($p = 0.026$ and $p = 0.003$, respectively).
CONCLUSION: The NLR, PLR, and RDW were not predictive in this study because we only included early- stage patients lacking lymph node involvement and the follow-up was short. In patients with renal cell carcinomas, the RDW and PLR increase with the tumor burden and predict poor prognosis *(Tab. 5, Fig. 1, Ref. 23)*. Text in PDF *www.elis.sk*
KEY WORDS: neutrophil/lymphocyte ratio, platelet/ lymphocyte ratio, renal mass.

Introduction

The cut-off value of the normal neutrophil/lymphocyte ratio (NLR) is 0.78–3.53 in individuals who do not smoke or drink alcohol, and in healthy non-geriatrics (1). However, the NLR is affected by age, race, steroid use, chronic disease, and depressive disorders. The autonomic nervous system, endocrine system (steroids, adrenaline, androgen, estrogen, thyroid hormones, and prolactin), and circulating mediators affect the NLR. Inflammatory responses by tumors and their microenvironments, necrosis, infection, the host immune and endocrine responses, and even cancer treatments play prognostic roles (2, 3). A low NLR may reflect subclinical or latent inflammation, or low-level stress (2). Neutrophils play roles in the immune response, tumor progression, and immune suppression (4). Cytokines released by tumors suppress neutrophils (4). The mean NLR is highest in white males and lowest in African Americans (2, 4). The pretreatment ratios in patients with prostate and breast cancer are lower than those of patients with other cancers (4).

Radiological imaging sometimes cannot differentiate between malignant and benign masses. Here, we retrospectively investigated whether inflammatory markers and tumor characteristics distinguished malignant and benign renal masses.

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Materials and methods

Patients diagnosed with malignancies via imaging or biopsy between September 2019 and January 2023, and who underwent partial/radical nephrectomy, were retrospectively analyzed. In total, 31 of 148 masses were benign and 117 were malignant. Trucut biopsy was performed in 30 cases. Partial/radical nephrectomy was performed for cases with malignant biopsies. The utility of the NLR, platelet/lymphocyte ratio (PLR), and red blood cell distribution width (RDW) for differentiation of malignant and benign renal masses was investigated.

We recorded patient age, body mass index (BMI), tumor location and histopathological type, benign/malignant status, tumor location within the kidney, T stage, pathological Fuhrman grade, and lymphovascular invasion (LVI) status. For staging, the TNM system of the American Joint Committee on Cancer (AJCC) was used (5). All patients underwent ultrasonography or computed tomography. Preoperatively, the NLR, PLR, and RDW were calculated using blood samples taken 1 month prior.

Inclusion criteria: Patients with renal masses detected ultrasonographically or via magnetic resonance imaging (MRI), and those whose malignant/benign status was not revealed by imaging. Final malignant/benign status was determined via biopsy or surgery.

Tab. 1. Demographic characteristics of patients.

Variables	Frequency (n)	Percent %
Gender		
Male	91	61.4
Female	57	38.5
BMI (body mass index)		
<18.9	1	0.6
18.5-24.9	38	26.0
25-29.9	68	46.5
>30	39	26.7
Biopsy		
Yes	30	20.2
No	118	79.7
Diagnosis		
Malign	117	79.0
Benign	31	20.9
Kidney localization		
Upper pole	52	35.1
Middle	39	26.3
Lower	35	23.6
Multifocal	22	14.8
Mass location		
Left kidney	72	48.6
Right	75	50.6
Nephrectomy type		
Partial	51	34.4
Radical	70	47.3
No surgery	27	18.2
Subtype of tumor		
Clear cell	87	75
Papillary	17	14.6
Chromophobe	12	10.3
Sarcomatoid	7	4.7
Grade		
1	14	9.4
2	42	28.3
3	36	24.3
4	11	7.4
no	34	22.9
Lymphovascular invasion		
Yes	7	4.7
No	125	84.4
T stage		
T1	75	50.6
T2	8	5.4
T3	29	19.5
Tx	5	3.3

Exclusion criteria: Metastatic patients, and those with granulomas and infections, autoimmune disease, or renal cysts.

Results

The mean age was 56 ± 12 years in the benign group and 58 ± 11 years in the malignant group. Ninety-one (61%) cases were male and 57 (39 %) were female. The mean tumor size was 4.95 ± 3.8 cm. Of the malignant cases, 87 (75 %) were clear cell, 17 (14.6 %) were papillary, and 12 (10.3 %) were chromophobe renal cell carcinomas (RCCs). Of the benign cases, 17 (54.8 %) were angiomyolipomas, 11 (35.4 %) were oncocytomas, 2 (6.4 %) were papillary adenomas, and 1 (3.2 %) was a fibrolipoma. Demographic data are shown in Table 1. In patients with malignancies, the mean NLR was ≤ 3.45 and > 3.46 (p = 0.903), the mean PLR was ≤ 142.8 and > 142.8 (p = 1.000), and the mean RDW was ≤ 43.5 and > 43.5 (p = 1.000), respectively. There were no differences between patients with malignant and benign masses (Tab. 2).

Tab. 2. Pre-operative cut off value of inflammatory markers .

Pre-operative cut off value		Diagnosis		Total	χ^2	p
		malignant	benign			
RDW	≤ 43.5	73	19	92	0.000	1.000
	<43.5	43	12	55		
Neutrophil	≤5701.6	77	23	100	0.374	0.541
	>5701.6	39	8	47		
Lymphocyte	≤2193.6	63	17	80	0.000	1.000
	>2193.6	53	14	67		
Platelet	≤265666.6	65	18	83	0.000	1.000
	>265666.6	51	13	64		
NLR	≤3.45	90	25	115	0.015	0.903
	>3.46	26	6	32		
PLR	≤142.8	77	20	97	0.000	1.000
	>142.8	39	11	50		

* p < 0.05; Chi-Square Test

The RDW, NLR, PLR, and lymphocyte count did not vary according to the BMI (all p > 0.05). The RDW and PLR were higher in females; the RDW was 44.7 ± 7.0 in women and 42.8 ± 6.7 in men, and the PLR was 165.2 ± 110 (p = 0.015) and 129 ± 74.3 (p = 0.002), respectively. There was no gender difference in the NLR or lymphocyte count (p = 0.978 and p = 0.748 respectively). The RDW, NLR, and lymphocyte count did not differ between patients with early and advanced disease (p = 0.057, p = 0.162, and p = 0.092, respectively) (Tab. 3). The PLR was significantly higher in patients with stage 3 malignancies, i.e., larger tumors (p = 0.011) (Tab. 3). The RDW, lymphocyte count, and NLR did not differ by T stage. The PLR differed between T3 stage patients and those in other T stages, as well as those with benign masses (p = 0.009) (Tab. 4). The RDW, PLR, and NLR did not differ among LVI grades 1–3, or according to the location of renal masses (right or left kidney, or both; or the upper, middle, or lower pole, or multicentric) (all p < 0.05). The predictive value of the RDW and PLR was examined according to tumor stage by drawing receiver operator characteristic (ROC) curves (p = 0.026 and p = 0.003, respectively) (Fig. 1). Optimal cut-offs were determined according to T stage. The RDW cut-off was 45.7 (sensitivity, 40 %; specificity, 82 %) and the PLR cut-off was 134.9 (sensitivity, 70 %; specificity, 70.5%) (Tab. 5).

Statistical methods

For all statistical analyses, SPSS for Windows software (version 22.0; SPSS Inc., Chicago, IL, USA) was used. The Shapiro-Wilk method was used to explore the normality of quantitative variables. As the data were not normally distributed, the Mann-Whitney U test and Kruskal-Wallis test were used to compare

Tab. 3. Comparison of RDW, lymphocyte, NLR, PLR values by stage.

Stage		N	Ort.+S.s	Med. (Min-Max	χ^2	p
	1	77	42.9±5.4	41.8 (35.8–66.4)		
RDW	2	8	41.4±3.4	40.1 (38.1–48.9)	5.728	0.057
	3	30	45.7±8.2	43.5 (37.9–79.0)		
	1	77	2287.9±876.8	2170 (510.0–4270.0)		
Lymphocyte	2	8	2351.2±704.4	2150 (1600.0–3640.0)	4.771	0.092
	3	30	1923±798.6	1800 (600.0–3920.0)		
	1	77	3.3±4.0	2.1 (0.7–25.5)		
NLR	2	8	2.2±0.7	2.4 (1.1–3.0)	3.634	0.162
	3	30	3.7±2.9	2.8 (1.3–15.4)		
	1	77	129.2±75.3	103.2 (61.6–498.0)		
PLR	2	8	129.7±43.9	130.3 (80.5–185.6)	9.014	0.011
	3	30	176.2±95.4	152.0 (34.3–491.6)		

*p<0.05; Kruskall-Wallis Test

Tab. 4. Comparison of RDW, lymphocyte, NLR and PLR values in malignant and benign cases according to T stage.

TNM: T Stage		N	Ort. ± S. s	Med. (Min-Max)	χ2	p
	Benign	31	43.4±9.1	41.3 (37.0 –90.3)		
	T1	74	43.1±5.4	41.9 (35.8-66.4)		
RDW	T2	8	42.1±3.8	40.1 (38.1–48.9)	4.692	0.320
	T3	29	45.7±8.3	43.5 (37.9 –79.0)		
	TX	5	41.6±2.7	41.3 (38.1–44.6)		
	Benign	31	2175.1±844.8	2050 (750.0 –4350.0)		
	T1	74	2291.4±893.8	2155 (510.0-4270.0)		
Lymphocyte	T2	8	2198.7±654.4	1900 (1600.0–3640.0)	4.870	0.301
	T3	29	1925.1±812.6	1800 (600.0 –3920.0)		
	TX	5	2408.0±325.9	2340 (1970.0–2820.0)		
	Benign	31	4.0±5.5	2.2 (0.9-29.7)		
	T1	74	3.3±4.1	2.1 (0.7–25.5)		
NLR	T2e	8	2.5±1.2	2.4 (1.1–5.1)	3.909	0.419
	T3	29	3.6±2.9	2.6 (1.3–15.4)		
	TX	5	2.0±0.7	1.6 (1.4–3.1)		
	Benign	31	150.1±121.9	119.7 (64.9–758.6)		
	T1	74	131.0±76.3	104 (61.6–498.0)		
PLR	T2	8	132.1±43.1	140 (80.5–185.6)	13.567	0.009*
	T3	29	177.9±96.6	154 (34.3–491.6)		
	TX	5	86.7±21.5	80.3 (61.4 –118.4)		

* p < 0.05; Kruskall-Wallis Test

groups (for non-categorical variables such as gender, BMI, stage, LVI, grade, kidney localization, tumor location). The comparison between NLR and PLR cut-off values between benign and malignant masses was evaluated with the chi-square test. ROC curves were drawn to evaluate the predictive value of the NLR, PLR and RDW, and to determine the optimal cut-off values. Subgroup analysis was performed according to tumor size and T stage. A two-tailed $p < 0.05$ was considered significant. We determined sensitivity, specificity, positive predictive value, negative predictive value, and accuracy using the following formulae: sensitivity = true-positives/ (true-positives + false-negatives); specificity = true-negatives/(true-negatives + false-positives); positive predictive value = true-positives/(true-positives + false-positives); and negative predictive value = true-negatives/(true-negatives + false-negatives). We performed the Spearman correlation test and a $p < 0.05$ was considered significant.

Discussion

High preoperative NLRs and PLRs are poor prognostic factors for mesothelioma, colon and hepatocellular cancers, and RCC (6). In a meta-analysis of 40,559 patients, a high NLR negatively impacted prognosis. The NLR increases during long-term chronic inflammation (3). However, the prognostic value of the PLR and RDW in patients with non-metastatic disease is limited (7). Neutrophil elevation inhibits the cytolytic effects of lymphocytes (3). An increase in the NLR is associated with more tumoral macrophages and higher levels of IL-6, -7, -8, -9, -12, and -17; and interferon (3). Although the prognostic value of the NLR varies by cancer type, it is lower for patients with early stage rather than metastatic cancers (3, 7).

No NLR, PLR, or RDW cut-off is available for healthy individuals (1). In our study, the cut-offs for benign masses were ≤ 3.45 and > 3.46 for the NLR, ≤ 142 and > 143 for the PLR, and ≤ 43.5 and > 43.6 for the RDW, thus not different for malignant and benign cases (Table 2). In the literature, an NLR for healthy individuals of 1.65 (range: 0.78–3.53) was reported (1). In another study, patients with benign and malignant thyroid nodules did not differ in terms of the neutrophil or lymphocyte count, or the NLR (8). Moreover, the NLR and PLR did not differ between patients with benign and malignant ovarian masses (9). The RDW for malignancy was reported as 45.7, with a sensitivity of 40 % and specificity of 82.4 % (p = 0.026), while the PLR cut-off was 134.9, with a sensitivity of 70 % and specificity of 70.5 % (p = 0.003). For patients with advanced-stage ovarian tumors, the PLR sensitivity was 59 % and the specificity was 72.7 % (10). Finally, the RDW was higher in patients with advanced stage and high-grade RCCs; the optimal cut-off was 12.8 % (sensitivity, 65 %; specificity, 51.5 %), and a higher RDW was an independent prognostic factor for cancer-specific survival (11, 12).

The lack of differences between our patients with malignant and benign masses is explained by the small sample and the fact that markers such as the NLR, PLR, and RDW are prognostic rather than predictive. There was no difference between patients with benign masses and early-stage carcinomas. Our follow-up period was 202 ± 172 days, and thus the period over which chronic inflammation was tracked was short. Although acute inflammation onsets quickly, chronic inflammation progresses slowly over months or years (13). Inflammatory markers levels measured before diagnosis of breast cancer were nonspecific and insensitive and are useful

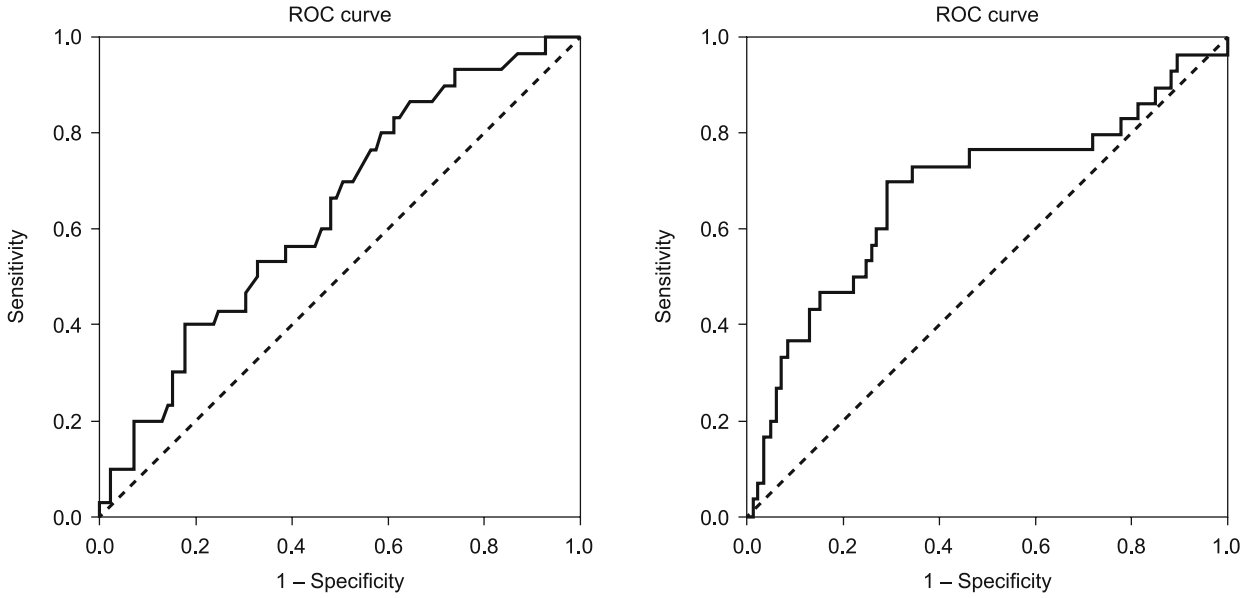

Fig. 1. A. Receiver operating characteristics (ROC) curves analysis of RDW predictive probability of tumor stage (p < 0.026) B. PLR predictive probability of tumor stage (p < 0.003).

only in advanced stages when the tumor burden increases (14). In some other cancers, increases in inflammatory markers levels require lymphoid tissue involvement (15, 16).

In this study, as the RDW and PLR increased with the T stage, their sensitivity and specificity became significant (p = 0.026 and p = 0.003, respectively) (Fig. 1). The PLR was significantly higher in patients with malignant than benign markers (p = 0.009) (Tab. 3). In prior studies, these markers were used to determine ovarian cancer-related mortality in patients with locally advanced and metastatic disease (7, 17).

The tumor subtype reflects tumor aggressiveness. Chromophobe and papillary clear cell tumors have a better prognosis than tumors with collecting duct and sarcomatoid differentiation (5). The tumor grade is a prognostic factor for distant metastases. Higher nuclear grades are inversely proportional to survival (5). The NLR and PLR indicate not only prognosis, but also tumor aggressiveness. High platelet levels are associated with a poor prognosis for localized RCCs (5). However, the value of the platelet level for identifying malignant masses has been little studied and may not be significant (18).

Seventeen of our benign cases had angiomyolipomas that are difficult to distinguish from RCCs via imaging studies. All masses involved blood, smooth muscle, and adipose tissue (19). All these cases were diagnosed via renal biopsy; only malignant cases underwent surgery. Thus, unnecessary procedures were avoided.

The limitations of our study include the retrospective design, small number of cases, short follow-up, and absence of inflammatory marker cutoffs for benign/malignant masses. The absence of lymphovascular and lymph node involvement in RCC patients may not affect inflammatory marker levels. We found no difference between benign and malignant masses using preoperative lymphocyte cut-offs of >2,193 and ≤ 2,193 (p < 0.05). In previous studies, NLR ≥ 5 was associated with significant suppression of the lymphoid response. In cases with mean lymphocyte values of 1.75 (10^9/L) and a neutrophil count of 4.25 (10^9/L), an increased NLR reflected an immature immune system response (20). Finally, the NLR and PLR were reportedly significantly higher in patients with metastatic lymph nodes (21, 22).

Inflammatory marker levels are affected by age, race, smoking, alcohol consumption, gender, chronic inflammation, myeloid dysfunction, nutritional status, and erythropoiesis (23). Increased production of erythropoietin and vitamin B12, and folic acid disorders that trigger bone marrow erythropoiesis, increase the RDW; therefore, this is the preferred prognostic marker for metastatic patients.

Tab. 5. RDW, PLR cut off values for malignancy.

RDW	Cut-off values	Sensitivity	Specificity
Optimal	45.7	40%	82.4%
Max. Sensitivity	37.7	100 %	7.1%
Max. Specificity	80	0	100 %
PLR	Cut-off values	Sensitivity	Specificity
Optimal	134.9	70 %	70,5 %
Max. Sensitivity	33.3	100 %	0
Max. Specificity	499	0	100 %

Conclusion

Inflammatory markers reflect immune system function. As early stage RCCs are not associated with lymphoid tissue reaction or chronic inflammation, the inflammatory marker levels of these patients were similar to those of our patients with benign masses. However, the RDW and PLR increased with the tumor burden and stage, indicating poor prognosis. In practice, inflammatory markers are preferred for evaluating the prognosis of metastatic disease; however, they do not accurately predict the courses of primary malignancies. Thus, marker prognostic value varies by tumor type and stage, disease duration, and cut-off value.

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